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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/050,888	01/14/2002	Raymond F. Gesteland	T9479.B	5912

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EXAMINER	
DEJONG, ERIC S	

ART UNIT	PAPER NUMBER
1631	

DATE MAILED: 02/03/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/050,888	GESTELAND ET AL.	
	Examiner	Art Unit	
	Eric S. DeJong	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 November 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-64* is/are pending in the application.

4a) Of the above claim(s) *See Continuation Sheet* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4,8,10,12,13,17,18,20,22,23,25,29,31,33,34,38,39,41 and 43* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Continuation of Disposition of Claims: Claims withdrawn from consideration are 3,5-7,9,11,14-16,19,21,24,26-28,30,32,35-37,40,42 and 44-46.

DETAILED OFFICE ACTION

Specification

The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code. Page 3, lines 8 and 9 of applicants response, filed 11/28/2005, containing an amendment to the instant specification fails to remove an embedded hyperlink from the instant specification as the listed address begins with the term "www", which is indicative of an active hyperlink. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

The previous objection to the specification as failing to provide proper antecedent basis for claimed subject matter under 37 CFR § 1.75(d)(1) is withdrawn in view of amendments made to the instant specification.

Claim Objections

The objection of claims 20 and 41 under 37 CFR §1.75(c) for being improper dependent claims is withdrawn in view of arguments presented by applicants.

Claim Rejections - 35 USC § 112, First Paragraph

The previous rejection of claims 4 and 25 under 35 USC § 112, first paragraph for lack of enablement is withdrawn in view of amendments made to the instant claims.

Claim Rejections - 35 USC § 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 18 and 39 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The phrase "in the range of about 0.01-0.50" recited in claim 18, line 2 and claim 39, line 2 is a relative term which renders the claim indefinite. The range of "0.01-0.50" must be taken in context with the claimed binary threshold function, however it is unclear from the instant claim if this particular range can be equivalently applied in instances wherein alternative binary threshold functions are utilized.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was

not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 2, 4, 8, 10, 12, 13, 17, 20, 22, 23, 25, 29, 31, 33, 34, 38, 41 and 43 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Matveeva et al. (IDS: Matveeva et al., Nature Biotechnology, 1998) taken in further view of Wu et al. (Nucleic Acids Research).

The instant claims are drawn to methods for predicting antisense activity of an oligonucleotide for down-regulating expression of a selected RNA comprising developing an artificial neural network on a computer-readable medium, mapping sequence motifs of preselected lengths in a nucleotide sequence of a test oligonucleotide complementary to a portion of a selected RNA, and obtaining output of the predicted antisense structure.

Matveeva et al. discloses several oligonucleotides that target various regions of C-raf mRNA and evaluate the binding efficiency of said oligonucleotides to C-raf mRNA taken in context of related antisense activity. See Matveeva et al., page 1374, column 2, line 12 through column 3, line 6 and Figure 1. Matveeva et al. additionally discloses the correlation coefficients between intracellular and in vitro data for the oligonucleotides. See Matveeva et al., page 1374, column 3, lines 7-50 and page 1375, figure 2A. The reference of Matveeva et al. is contained in a publication of the scientific journal "Nature Biotechnology". Further, Matveeva et al. discloses over 20 oligonucleotides with

established *in vivo* antisense activity. See page Matveeva et al., 1375, Figure 2A-C. An oligonucleotide that was not complementary to the C-raf mRNA was also used as a control. See Matveeva et al., page 1374, Figure 1.

Matveeva et al. further discloses that research establishing antisense activity for some oligonucleotides is only a step toward the challenging prospect of being able to predict antisense activity in cells using simplified model systems and that such data must be obtained and further analyzed with statistical methods for the future practical use of such assays. See Mateeva et al., page 1375, column 2 line 3 through column 3, line 4. However, Mateeva et al. does not fairly teach the method of using or making artificial neural network systems for predicting the above described antisense activity of oligonucleotides for down-regulating expression of selected RNA as set forth in the instant claims.

Wu et al. discloses the methodology of using and developing an artificial neural network system for rapid and accurate classification of ribosomal RNA sequences according to a phylogenetic relationship. See Wu et al., Abstract. Further, Wu et al. discloses that the major application of such neural networks is the rapid sequence annotation and automated family assignment which is a tool that is generally applicable to any databases that are developed according to family relationships. Such neural network designs are disclosed as being easily extended to the task of analyzing other nucleic acid sequences. See Wu et al., page 4298, column 2, lines 13-42.

Wu et al. discloses that the systems and software for the neural network have been ported to several different computer platforms and computer languages. See Wu

et al., page 4293, column 2, lines 42-57. The disclosed neural network system is configured as a three layer network comprising an input layer, a hidden layer, and an output layer each containing a variable number of nodes. See Wu et al., Figure 1 and page 4292, column 1, lines 20-32. A nucleic acid sequence is first converted by an encoding method into a neural net input vector, and the neural network then maps the sequence vectors into predefined classes according to sequence information embedded in the neural interconnections after network training. See Wu et al., see Figure 1 and page 4292.

Wu et al. discloses in Figure 1 at least 4 nodes in the hidden layer that under a reasonably broad interpretation is comprises about 4 nodes. Additionally, Wu et al. discloses that in counter-propagation neural network, the number of nodes in the hidden layer is dynamically controlled and can be added to in order to optimize pattern recognition in the system. See Wu et al., page 4293, column 2, lines 13-41. Wu et al. discloses in Figure 1 that the output layer is comprised of a variable number of individual nodes output nodes. Since individual nodes make up the out put layer, a reasonably broad interpretation is that the output layer comprise one output node as instantly claimed.

Wu et al. further teaches an embodiment of the sequence classification/clustering system of the neural networks include a back propagation neural network, which includes a momentum term. However, the values of the momentum term are varied between –0.3 and 0.3 to optimize a particular neural network system. A momentum term of 0, which is an embedment of the disclosed system, would reasonably be

construed as a back propagation algorithm and read on the claims neural network using a back-propagation algorithm without a momentum term. See Wu et al., page 4293, column 1, lines 40-56. Wu et al. cites the additional reference Wu et al. (Protein Science) in support of the above methodology of using a back propagation algorithm. See Wu et al., Protein Science, page 669, column 1, lines 25-36. Wu et al. discloses that the systems and software for the neural network have been ported to several different computer platforms and computer languages (an artificial neural network embodied on a computer-readable medium). See Wu et al., page 4293, column 2, lines 42-57.

The instant specification discloses an example of how output data may be normalized utilizing a function that forces the result to lie in the range of 0 to 1. See the instant specification, page 22, lines 10 and 11. Relying on this example, the examiner has construed that a reasonably broad interpretation of normalization is a function or operation that rescales a data to the range of 0 to 1. Wu et al. in Figure 1 demonstrates that sequence data converted into a compressed input vector wherein amplitude values are made to conform to a range of 0 to 1.

Therefore it would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains to apply the methods and assays for establishing antisense activity for oligonucleotides, as taught by Mateeva et al., in combination with the artificial neural network system for rapid and accurate classification of RNA sequences, as taught by Wu et al., because Wu et al. further teaches that the major application of neural networks is the rapid sequence

annotation and automated family assignment that is generally applicable to databases developed according to family relationships.

Response to Arguments

Applicant's arguments filed 11/28/2005 have been fully considered but they are not persuasive.

In regards to the rejection of claims 18 and 39 under 35 USC §112, second paragraph, applicants argue that the values used in the range "0.01-0.50" are unitless and that a person skilled in the art would understand that the binary threshold function indicia are unitless.

Claims 18 and 39 each recite the limitation of the "range of about 0.01-0.50" as a threshold cut-off value applied to a binary threshold function. However, the instant claims do not recite a specific function that the claimed range is to be applied, but rather generically recite "a binary threshold function". Applicants argument does not resolve the existing ambiguity, specifically if the recited range equivalently applies to any given binary threshold function selected for use in the claimed method. Upon review of the specification, no specific definition has been disclosed wherein only one particular binary threshold function is to be used in conjunction with the disclosed method. It is noted that a single specific 3-way threshold function has been provided (see the instant specification, page 25, lines 8-14 and equation (6)), but this exemplary embodiment does not serve to limit the scope of the claimed "binary threshold function" to the disclosed function. As such, the claimed range remains ambiguous as it is unclear if the

range equivalently applies to every binary function that may be used in the claimed method.

In regards to the rejection of claims 1, 2, 8, 10, 12, 17, 22, 23, 29, 31, 33, 38, and 43, applicants argue that Mateeva et al. and Wu et al. have similarities to the instantly claimed invention, but each reference individually is vastly different from the claimed invention. Further, applicants refer to Wu et al., page 4298 in support as to why the combination of Mateeva et al. and Wu et al. is not obvious (see applicants response, filed 11/28/2005, page 32, line 8 through page 35, line 13). Applicants additionally assert that the present rejection is basically an argument that it would obvious to try or experiment with neural networks to arrive at the instantly claimed method (see applicants response, page 36, line 13 through page 37, line 11).

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Further in response to applicant's arguments regarding the obviousness rejection and motivation to combine the reference, the fact that applicant has recognized another advantage which would flow naturally from following the suggestion of the prior art cannot be the basis for patentability when the differences would otherwise be obvious. See *Ex parte Obiaya*, 227 USPQ 58, 60 (Bd. Pat. App. & Inter. 1985). Further,

applicants argument does not address the motivation to combine the cited references.

In regards to the combination of references, the previous Office action, page 8, lines 11-20, stated:

> "Mateeva et al. further discloses that research establishing antisense activity for some oligonucleotides is only a step toward the challenging prospect of being able to predict antisense activity in cells using simplified model systems and that such data must be obtained and further analyzed with statistical methods for the future practical use of such assays. See Mateeva et al., page 1375, column 2 line 3 through column 3, line 4. However, Mateeva et al. does not fairly teach the method of using or making artificial neural network systems for predicting the above described antisense activity of oligonucleotides for down-regulating expression of selected RNA as set forth in the instant claims."

Applicants cite page 4298 of Wu et al. as in support of the argument that "it was not obvious that the neural network approach would be applicable or feasible in going from protein sequence phylogenetic classification to nucleic acid sequence phylogenetic classification". However, applicants argument does not appear to be consonant with the cited portion of Wu et al. To the contrary, the citation indicates that the disclosed use of neural networks for phylogenetic classification provide a significant improvement of the use of known methods such as Fasta and Blast. For example, Wu et al., page 4298, col. 1, lines 20-22 states:

> "The neural network method compares favorably, in terms of both accuracy and speed, to other methods currently available for phylogenetic classification of rRNA sequences."

Wu et al., page 4298, col. 1, lines 48-50 further states:

> "The neural network classification accuracy is significantly better than that of the Blast or Fasta database search methods, probably due to the high degrees of similarities among rRNA sequences."

Further, it is acknowledged that Wu et al. specifically teaches that result of direct comparison between Similarity Rank and neural network methods for phylogenetic classification should be interpreted with caution (see Wu et al., page 4298, col. 1, lines 37-47). However, this teaching does not indicate that the application of neural networks to phylogenetic studies cannot be successfully applied. One this point, Wu et al. (page 4298, lines 33-42) teaches that the disclosed methods have are generally applicable to elucidating such familial relationships:

> "The neural network tool is generally applicable to any databases that are developed according to family relationships because neural network employs a "supervised" learning algorithm. The designs of the neural network system can be easily expanded to classify other nucleic acid sequences. Preliminary studies have been conducted to classify DNA sequences (containing both protein encoding regions and intervening sequences) directly into protein superfamilies with satisfactory results. It is, therefore, possible to develop a gene identification system that can classify indiscriminately sequences DNA fragments."

Applicants further Argue that Mateeva et al. and Wu et al. fails to teach or disclose each and every feature of the presently claimed invention (see applicants response, page 35, line 14 through page 36, line 12. However, applicant's arguments fail to comply with 37 CFR 1.111(b) because they amount to a general allegation that the claims define a patentable invention without specifically pointing out how the language of the claims patentably distinguishes them from the references. Therefore applicants argument is not found persuasive.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry of a general nature or relating to the status of this application should be directed to Legal Instrument Examiner, Tina Plunkett, whose telephone number is (571) 272-0549.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Eric S. DeJong whose telephone number is (571) 272-6099. The examiner can normally be reached on 8:30AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel, Ph.D. can be reached on (571) 272-0718. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for

published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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EDJ EDJ

JSB 31 January 2006
JOHN S. BRUSCA, PH.D
PRIMARY EXAMINER